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Review Article

Liver transplantation for the treatment of nodular regenerative hyperplasia

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ABSTRACT

Background: Nodular regenerative hyperplasia (NRH) is the leading cause of non-cirrhotic portal hypertension in Western countries. Although some patients are successfully managed medically or with shunting procedures, others require liver transplantation. The aim of this review was to assess the overall results obtained with liver transplantation and to better define its role in this setting.
Methods: Systematic review of all published studies on liver transplantation for NRH without language restrictions, in Medline, Embase and Cochrane Library databases through March 2010.
Results: 17 studies including a total of 73 patients were identified; 47 (64.3%) were excluded due to lacking inclusion criteria or clinical data and 26 (35.7%) were analysed. Before liver transplantation, the most frequent clinical presentation was gastroesophageal bleeding (65.3%) followed by ascites (61.5%), hepatic encephalopathy (30.7%) and liver failure (11.5%). The mean follow-up reported after liver transplantation was 30.6 ± 27.6 months and patient and graft survival rate was 78.3%. Only one case reported a NRH recurrence 7 years after liver transplantation (LT).
Conclusions: Although there are no hard data supporting the role of liver transplantation in symptomatic NRH, onset of severe portal hypertension in this setting may represent a valid indication.

1. Introduction

Nodular regenerative hyperplasia (NRH) is a rare chronic liver disease, potentially evolving to non-cirrhotic portal hypertension [1]. NRH was first described by Steiner [2] and has an incidence of 2.5% in post-mortem studies [3,4] and 0.5% in liver biopsies [2]. Six percent of liver biopsies performed in potential living liver donors detected NRH [5].

NRH represents the end manifestation of the chronic liver damage caused by a spectrum of systemic diseases; it consists of a diffuse liver micro-nodular transformation as a reflection of progressive degrees of hepatic portal venopathy [6]. The pathogenesis seems to include chronic hepatic ischemia caused by phlebitis and thrombosis of small portal veins which results in hyperplasia of acini with preserved arterial blood flow [7,8]. The ischemia leads to atrophy and apoptosis and a compensatory hyperplasia and regenerative nodules in the unaffected areas [9,10].

NRH is a pathological finding that describes a liver with multiple small nodules and minimal or no hepatic fibrosis [11,12]. The nodules are composed of hepatocytes, usually in double-cell plates, hyperplastic in some areas and atrophic in others [13–16]. No other non-invasive diagnostic tools demonstrated a sufficient sensibility and specificity for the diagnosis of NRH [18–20].

Although NRH is asymptomatic in most of the cases, portal hypertension stigmata [21–24] represent the end manifestation of the disease requiring liver transplantation (LT) [3,25,26]. It seems likely that most patients with 'idiopathic' portal hypertension have NRH although this point may still be debatable [27,28].

Although the cause of NRH is not yet fully understood, NRH seems to be a secondary effect of a hypercoagulable state associated with several other diseases [28–32]. Most of these aetiologies exert their effects by modifying liver inflow and outflow [33–35], altering the small portal and hepatic microcirculation and stimulating the ischemia/regeneration process as mentioned above [24]. Examples have been described in several human immunodeficiency virus (HIV)-infected patients with symptomatic non-cirrhotic portal hypertension [28,36–48]. In fact, NRH has been associated with haematological disorders such as myeloproliferative [24] and lymphoproliferative diseases [24,29–31,49–54], polycythemia, hyperhomocysteinemia, primary hypogammaglobulinemia and common variable immunodeficiency [55]; systemic autoimmune diseases such as systemic lupus erythematosus [56,51], rheumatoid arthritis [57], anti-phospholipid syndrome, scleroderma [58], progressive systemic sclerosis, Sjogren's syndrome [59], polyarteri-

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tis nodosa, chronic granulomatous disease, Felty's syndrome [60]; immunosuppressive drugs as azathioprine [61–66] and systemic chemotherapy [67–69].

NRH was also described with primary coagulopathies such as anti-cardiolipin and anti phospholipid antibodies or factor V Leiden mutations [70–72] and in Turner's syndrome [73,74]. Histological patterns similar to NRH were found in explanted liver in patients who underwent LT due to Budd Chiari syndrome [75].

Some authors believe that the prognosis in patients with NRH is related more to the severity of the underlying systemic disorder than to hepatic involvement [25]. Others believe that the prognosis depends on the existence and severity of portal hypertension, which occurs in about 50% of cases, either as a presenting symptom or as a late complication [3].

Treatment for NRH should involve the correction of the hypercoagulable state [76] and should be focused on portal hypertensive complications [i.e. beta-blockers, variceal ligation and/or portosystemic shunts (TIPS)] [24]. LT must be considered only in cases showing severe portal hypertension and/or liver failure [77–79]. Anecdotal reports [33,44,62,72,77–85] and a recently illustrated series from the European Liver Transplant Registry suggest that LT may be a valuable treatment for severe NRH complicated by gastrooesophageal bleeding or cholestatic cirrhosis.

The aim of this review was to assess the overall results obtained with LT for symptomatic NRH and to possibly clarify the indications and limitations in this setting.

2. Materials and methods

2.1. Study selection and data extraction:

Published studies that described LT as treatment for NRH were searched for and selected in the MEDLINE, EMBASE and Cochrane Library databases using as key words "nodular regenerative hyperplasia", "liver transpl*", "hepatic transpl*" without language restrictions. NRH was defined as multiple regenerative nodules not surrounded by a collagen rim and usually no larger than an hepatic lobule or less than 3 mm [4,11,12,17]. Exclusion criteria consisted in articles that described NRH on a background of cirrhosis or those in which Focal Nodular Hyperplasia (FNH) or Incomplete Septal Cirrhosis (ISC) coexisted in the histological diagnosis of the explanted liver. We also excluded those articles that reported the histological evidence of NRH on explanted livers after LT when the main indication for transplantation was end-stage liver disease not related to NRH (e.g. Budd Chiari Syndrome [75]). Patients with NRH who did not undergo LT were not considered for the main analysis. Potentially relevant studies were identified by the title and the abstract and full papers were obtained and assessed in detail. A specifically designed data form was used to collect all relevant data, including details of the experimental design, patient demographics, technical aspects, outcome measures and complications. Data collection was carried out independently by two researchers and then compared. Outcomes analysed were the indications for LT as well as patient survival rates.

2.2. Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences Windows version 13.0 (SPSS, Chicago, Illinois, USA). Descriptive statistics for qualitative variables were performed with occurrences and described with relative frequencies. The survival rate was calculated using Kaplan–Meyer methods and p values < 0.05 were considered significant.

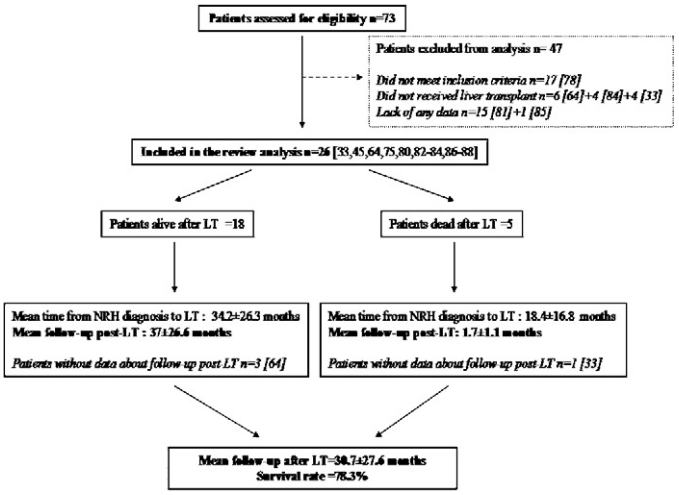

Fig. 1. Study screening and outcomes of evaluated patients.

3. Results

We identified 17 studies including a total of 73 patients [33,44,62,72,75,77–85]. Forty-seven (64.3%) of these were excluded from the analysis because they did not receive LT ($n = 14$) [33,62,81] or due to the lack of inclusion criteria ($n = 17$) [75] or significant clinical data ($n = 16$) [78,82]. The study screening and outcomes of evaluated patients are illustrated in Fig. 1. From 11 studies [33,44,62,72,77,79–81,83–85], 26 (35.6%) patients were included in the present review because they were transplanted due to NRH. The earliest case was described in 1990 [85] and the most recent series in 2008 [44]. Clinical features, liver disease stage before LT and outcome are summarized in Table 1. Nineteen (73%) patients were males and 7 (27%) were females. Mean age at diagnosis was 43 ± 10.8 years old. Mean post-LT follow-up was 37 ± 26.1 months. All cases presented a symptomatic NRH liver disease. The most frequent clinical manifestations were bleeding from gastrointestinal varices (17/26; 65.3%) followed by ascites (16/26; 61.5%), encephalopathy (8/26; 30.7%) and spontaneous bacterial peritonitis (1/26; 3.8%). Three patients (3/26; 11.5%) presented liver failure on account of NRH developed after their first LT due to non NRH-related diseases [62]. They received azathioprine therapy until NRH diagnosis which was then stopped. Treatments chosen to treat gastroesophageal bleeding before LT were endoscopic band ligation (3/26; 11.5%) [44,77,83], sclerotherapy (7/26; 26.9%) [77,79,81,84], surgical portacaval shunt (1/26; 3,8) [81] and transjugular intrahepatic portosystemic shunt (TIPS) (3/26; 11.5%) [79,80,83]. Repeated paracenteses were performed in 2 (7.6%) patients [80,84]. Partial or re-canalized portal vein thrombosis was detected before LT in 9 (34.7%) patients [33,44,72,77,79,80,85]. The mean time between the diagnosis of NRH and LT was 27.3 ± 24.8 months. Mean Child-Pugh and MELD scores at time of NRH diagnosis and at LT were 8.6 ± 2.5 and 9.5 ± 3.2 and 8.1 ± 1.3 and 14.7 ± 3.6 [MELD scores at surgery were available only in 12 (46.1%) transplanted patients] respectively. The 5-year patient and graft survival rate was 78.3% (Fig. 2).

Only one case developed NRH recurrence 7 years after LT [79]. Four (15.3%) received a combined renal and liver transplantation [79,81,84]. One of the dead patients underwent a second LT due to hepatic artery thrombosis and died during the third LT performed for intractable ascites [33]. One patient died by suicide 3 months after a successful LT [79]. Two patients died within 6 months of LT due to infectious systemic diseases, the first due to Herpes Zoster Virus encephalitis and the second due to pseudomonas sepsis [33,85]. One patient died due to the rupture of a splenic artery

Table 1
Clinical features at liver transplantation and transplant outcome of patients transplanted for nodular regenerative hyperplasia-related liver disease.

Authors	Year	*n*	Age/Gender	Clinical manifestation	CHP-LT	MELD-LT	Complications after LT	F-U months	Status
Mc Donald et al. [85]	1990	1	47 M	ASC-HE-SBP	–	–	HZV encephalitis	4	D
Elariny et al. [84]	1994	1	44 F	ASC-BEV	–	–	–	24	A
Gane et al. [62]	1994	3	23 M	DLF	C (11)	–	–	–	A
			20 F	DLF	B (7)	–	–	–	A
			28 F	DLF	B (7)	–	–	–	A
Loinaz et al. [79]	1998	4	37 M	BEV-ASC	B (8)	16	AR, NRH rec	84	A
			41 M	BEV	A (7)	23	Cirrhosis HCV	65	A
			37 M	BEV-ASC	C (10)	16	–	3	D
			25 M	BEV-ASC	B (9)	17	Splenic aneurism rupture	1	D
Dumortier et al. [81]	1999	2	59 M	ASC-HE	B (9)	17	–	33	A
			40 M	ASC	B (7)	13	–	10	A
Radomski et al. [80]	2000	4	45 M	ASC-HE	–	–	CMV pneumonia	48	A
			48 M	BEV-HE	–	–	–	46	A
			54 M	ASC	–	–	–	43	A
			39 F	BEV-ASC-HE	–	–	Pancreatitis	24	A
Dumortier et al. [77]	2001	3	49 M	ASC-BEV	B (7)	11	–	102	A
			41 M	BEV	B (8)	14	–	24	A
			63 M	ASC-BEV-HE	B (9)	16	–	48	A
Jawaid et al. [83]	2003	1	51 M	BEV	–	–	–	24	A
Buchel et al. [72]	2005	1	51 M	HE	–	–	ANFH	24	A
Devarbhavi et al. [33]	2007	3	55 F	ASC-BEV	–	–	HAT, Re-LT	–	D
			56 M	ASC-BEV	–	–	Sepsis	1	D
			48 M	ASC-BEV	–	–	–	48	A
Tateo et al. [44]	2008	3	38 F	ASC-BEV	–	12	–	9	A
			43 M	ASC-BEV	–	9	–	7	A
			38 F	BEV	–	13	–	4	A

F-U: follow-up; M: male; F: female; LT: liver transplant; CHP: Child-Pugh score; MELD: Model End-Stage Liver Disease; DLF: deranged liver function; NRH: nodular regenerative hyperplasia; ASC: ascites; HE: hepatic encephalopathy; SPB: spontaneous bacterial peritonitis; BEV: bleeding from esophageal varices; ANHF: avascular necrosis of the femur head; HAT: hepatic artery thrombosis; AR: acute rejection; D: dead; A: alive.

aneurism 2 weeks after LT [79]. Postoperative complications were overall reported in 10 patients (38.4%) (Table 1).

4. Discussion

Despite NRH being a well-known liver disorder [28], the optimal management is still unknown, mainly due to the rarity of the end-stage liver disease phase and the limited availability of published data. Most cases of NRH occur in patients with a previous history of prolonged and asymptomatic long-standing systemic diseases [24,29–31,49–60]. In such cases the management aims to treat the underlying disorders [3,24,53] and to remove any potential etiologic agent, such as chemotherapy (i.e. 6-Thioguanine, Busulfan, Doxorubicin, Cyclophosphamide, Chlorambucil, Cytosine arabisonide, Bleomycin, Carmustine) [67,68] or azathioprine-based immunosuppressive therapy [33,61–66].

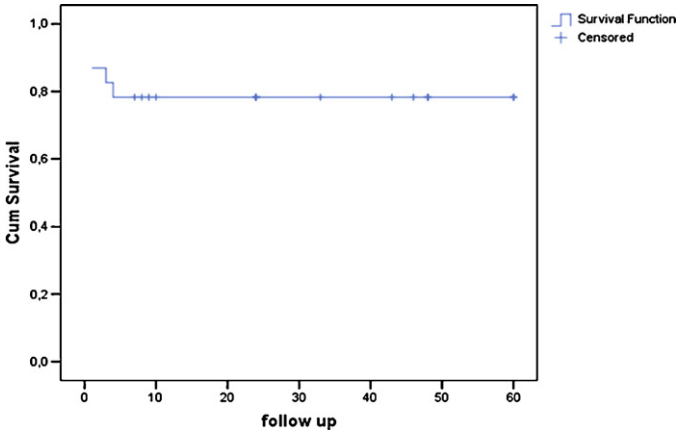

Fig. 2. Survival analysis according to Kaplan–Mayer model.

Because more than 50% of NRH cases are complicated by a symptomatic portal hypertension, the treatment should also aim to control the clinical manifestations of portal hypertension, considering LT as a definitive long-term treatment [21]. The treatment of variceal bleeding and ascites does not differ from that recommended for cirrhotic patients [44,77,79–81,83,84]; beta-blockers [81] or endoscopic treatments [44,77,79,81,83,84] have been described as an initial attempt to control symptomatic variceal bleeding and, when necessary, surgical porto-caval shunt is also a good option [81,84]. Furthermore, in the specific setting of NRH-derived portal hypertension, radiological interventions such as TIPS seem to be more useful than for the treatment of cirrhotic portal hypertension [44,79,80,83,84]. Nonetheless, in the worst scenario, namely when the whole liver is dramatically scattered by multiple diffuse nodules in a cirrhosis-like [62] fashion and/or portal hypertension occurred [33,44,72,77,79–81,83–85] the only possible strategy is to remove the native liver.

The goal of the present study is to scrutinize all cases of LT performed for NRH and reported so far, in order to investigate the role that LT may have in the treatment of NRH.

We identified 26 patients (Table 1) liver transplanted due to symptomatic or end-stage NRH.

The 5-year patient and graft survival rate was 78.3%. This result seems to be very similar to that reported for other LT indications in Europe [86,87]. Data from literature show an overall mortality rate of 19.2% (5/26 patients) with deaths occurring within the first six post operative months. NRH recurrence after LT is documented in only one case transplanted 7 years previously due to NRH and treated with azathioprine for an episode of acute rejection [79].

These data, though anecdotal, suggest that onset of NRH-end-stage liver disease or NRH-derived portal hypertension may represent a valid indication for LT.

Regarding other indications for LT, recent analyses have shown a survival benefit only for patients with MELD scores above 15 at the time of transplantation [87–89]; however, there is still debate

Table 2
Clinical features, liver disease stage and outcomes of patients with nodular regenerative hyperplasia who did not undergo liver transplantation.

Authors	Year	*n*	Age/gender	Clinical manifestation	PH treatment	CHP	MELD	F-up (months)	Status
Gane et al. [62]	1994	6	19 F	BEV	–	A(6)	–	6	A
			37 F	ASC	–	B (8)	–	6	A
			41 F	–	–	A (5)	–	6	A
			53 M	–	–	A (5)	–	6	A
			27 M	ASC	–	B (7)	–	6	A
			55 F	–	–	B (9)	–	6	A
Dumortier et al. [81]	1999	4	40 M	BEV	SLC-MCS	A (5)	5	132	A
			38 M	–	–	A (5)	4	102	A
			28 M	–	BB	A (6)	4	63	A
			33 M	BEV	BB-SLC	A (5)	5	60	A
Devarbhavi et al. [33]	2007	4	18 M	ASC	–	–	–	–	D
			25 F	ASC	–	–	–	–	D
			30 F	ASC	–	–	–	–	A
			47 M	ASC-BEV	–	–	–	–	A

M: male; F: female; NRH: nodular regenerative hyperplasia; PH: portal hypertension. BEV: bleeding from esophageal varices; ASC: ascites; SCL: sclerotherapy; BB: beta-blocker (propanolol); D: dead; A: alive; LT: liver transplant; CHP: Child-Pugh score; MELD: Model End-Stage Liver Disease; MCS: mesenteric-cava shunt.

on whether MELD score is always an adequate representation of the severity, complexity and risks associated with a heterogeneous disease requiring LT.

Although the median MELD score at time of LT in NRH patients was 15 (range: 9–23), and therefore not too far from the value considered suitable for the other indications for LT, the main indication of LT in this setting is given by portal hypertension complications. Thus, NRH should be considered an "exception" to the MELD rule and the stigmata of portal hypertension should be considered the true indication for LT.

The small number of patients transplanted for NRH and the wide range of MELD scores (9–23) at time of LT, unfortunately do not allow to estimate the survival benefit attributable to LT.

The evaluation of transplant benefit of LT for NRH is also difficult due to the lack of published studies with an adequate follow-up, including patients with NRH who did not undergo LT. We were able to analyse only the patients included in the studies considered in the present review who did not undergo LT [33,62,81]. The main characteristics and results of patients with NRH but who did not undergo LT are summarized in Table 2. These show a survival rate of 85.8% at a mean follow-up of 39.3 ± 47.3 months. MELD scores were available for only 4 patients, but the median Child-Pugh score was only 6 (range 5–9). Thus it is likely that the lower stage of liver disease justifies the reported good survival without LT.

In conclusion, the existing data on patients transplanted for NRH show that NRH can be considered as an "exception" to the MELD rule whereas portal hypertension should be considered the main indication for LT. The transplant benefit of LT due to NRH cannot be estimated at present. However it is conceivable that transplant benefit may exist for NRH cases with symptomatic portal hypertension with poor response to modern treatments or for patients with decompensated liver disease.

Conflict of interest statement
None to report for all authors.

List of abbreviations

LT, liver transplantation; MELD, Model for End-stage Liver Disease; NRH, nodular regenerative hyperplasia; TIPS, transjugular intrahepatic portosystemic shunt.

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